CERTIFICATE OF TRANSLATION

I, the undersigned, hereby certify

that I am well acquainted with the English and Japanese languages,

that I prepared the attached document, and

that, to the best of my knowledge and belief, the attached document is an accurate translation of the Japanese patent application JP 2004-100186 filed on March 30, 2004.

I declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true.

Keiko Sasada
Keiko SASADA

January 14, 2010
Date

[Name of the Document] Specification

[Title of the Invention] MEDICAL MATERIAL, MEDICAL INSTRUMENT USING THE SAME, AND METHOD FOR FABIRICATING MEDICAL MATERIAL

[Field of the Invention]

The present invention relates to a medical material which is in contact with a living body or organic component, and exhibits excellent biocompatibility for a long term, a medical instrument using the medical material, and a method for fabricating the medical material.

[Background Art]

Increasing attention has been drawn not only to medical instruments for diagnosis, e.g., conventional angiography, but also to medical instruments, such as a catheter, guide wire, and stent, used for various highly-advanced medical treatments called as intravascular treatment, such as, expansion of artificial organs and stenotic vessels, excision of aneurysm of aorta, and administration of anticancer agents. As a material for satisfying properties, such as mechanical properties, shape retaining properties, and durability, which are required for these medical instruments, inorganic materials, e.g., stainless and ceramics, have been used.

On the contrary, with advance of medical technology, an opportunity in which these medical instruments are in contact with body tissue and blood has been increasing. Problems that medical instruments cause damages to body tissue or allow blood to clot are occurring. Therefore, biocompatibility of a medical material used for a medical instrument has received a lot of attention. A lot of attention has also been focused on a material having a component having living-body responsiveness controlling functions of body tissue by controlling physical and chemical properties of a surface of a material.

In order to prevent blood clot formation occurring when a medical material and blood are in contact with each other, an expensive anticoagulant such as patulin is subsequently administered. However, a long term administration of patulin causes problems of disorder of

lipid metabolism, prolonged bleeding time, decrease of platelets, and allergic reaction, or the like. Also, there are problems that biological molecule such as patulin of animal origin may cause infection diseases, and there is a high possibility that the use of the biological molecule may be limited in the future. Patulin is configured to be gradually released with time to maintain anticoagulability, and therefore, it is difficult to maintain anticoagulability for a long time. Patulin strongly inhibits coagulation protein thrombin to exhibit anticoagulability by a complex formation with anchitoronbin (ATIII). Therefore, it is indicated that there are various problems, e.g., a problem that it cannot be expected that Patulin does not have an effect on patients who is congenitally lacking ATIII. The improvement of the problem is needed.

On the contrary, it has been considered that a membrane having a biocompatible component, e.g., collagen, is formed on a surface of a medical material to impart biocompatibility to the surface, thereby preventing blood clot due to the medical material. However, when forming such a membrane, there is a problem that adhesion between the membrane and the coated layer cannot be maintained for a log term.

In a field of cell engineering, there have been studies on regeneration of tissue by an *in vitro* control of differentiation of a cell, cell reproduction, and cell organization. Attention has been drawn to a material controlling release of factors for cell differentiation or cell reproduction by temporal or spatial induction, and a material that is convenient for bonding cells and cell reproduction, and that causes no damages to cells when the cells are separated from the base material after cell reproduction. To obtain such materials, it is necessary to form a structure that is to be a good base for adhesion of cells on surfaces of organic or non-organic materials by controlling a three-dimensional shape with use of micro- or nano-level material technologies, form a meshwork so that factors for cell reproduction or cell differentiation, or nutrition can be smoothly moved, and perform a surface treatment.

In view of the above, a method of modifying a surface of a medical material with a

biocompatible component has been conducted to provide biocompatibility, such as antithrombogenicity, etc., to the surface of the medical material that is in contact with a living body or organic component. For example, a hydrogel layer similar to the surface of a biomembrane can be formed on the surface of a medical material by modifying the surface of the medical material with a polymer containing as one component an artificial material having a chemical structure similar to the components of the biomembrane, such as 2-methacryloyl-oxyethyl phosphorylcholine (MPC), o-methacryloyl-L-Serine (SerMA), or the like, whereby excellent biocompatibility can be given to the surface of the medical material.

A method of modifying a surface of a medical material with a biocompatible component or a component having living-body responsiveness includes a physical modification, such as coating or impregnation, and a chemical modification, such as immobilization by using graft polymerization, covalent bond, ionic bond, or the like. Although the physical modification is simple, it is difficult to obtain a medical material which exhibits stable biocompatibility for a long term since the biocompatible component is likely to separate from the surface of the medical material.

On the contrary, when using the chemical modification, the separation of the biocompatible component from the surface of the medical material can be suppressed. However, a surface of an inorganic base material often used as a base material for medical material, e.g., a metal material, ceramic material, does not contain an organic layer necessary for forming a free radical, a responsive functional group. Therefore, the surface of the base material cannot be directly chemically modified.

Although it is possible to coat a surface of a metal or ceramic material, or the like, with macromolecular resin exhibiting a characteristic of forming a coating film to chemically bond the biocompatible component on the surface, this case has a problem that a small molecule compound harmful for a living body included in a macromolecular resin for forming a coating

film elutes from the surface of the coating film. Also, there is a problem that since the bond between the coating film and the base material is weak, the macromolecular resin is separated from the surface of the base material, and it is difficult to uniformly form the coating film on the surface of the base material.

An organic base material, such as a macromolecular resin, or the like, has a biocompatible component, and can chemically modify the surface of the base material. However, there has been a problem that the base material itself is hydrolyzed by an organic component to be deteriorated. It is difficult to obtain a medical material which exhibits stable biocompatibility for a long term.

As a method for imparting a medical material, a method of coating a surface with a diamond-like carbon film (DLC film) has been known (see, e.g., Patent Document 1). The DLC film is strongly bonded to the base material to form a fine film. Therefore, the DLC film hardly separates from the base material. Since the DLC film is a very smooth and chemically inert film, the DLC film is less likely to react to organic component.

[Patent Document 1] Japanese Laid-Open Patent Publication No. 10-248923

[Non-Patent Document 1] Haruo Ito et al., "Biomaterial", 1985, Vol. 3, pp. 45-53

[Disclosure of the Invention]

[Problems that the Invention is to solve]

However, although coating a surface of a base material with a DLC film imparts durability to a medical material, the DLC film does not positively gives biocomparibility to the medical material since the DLC film exhibits high hydrophobicity. The DLC film introduced into a living body is recognized as a foreign substance, thereby causing a problem that reactions in which antigen-antibody reaction, phagocytosis, loculation, inflammation, and neoplastic transformation are intricately combined with one another cause to a living body (see Non-Patent Document 1).

The present invention provides a solution to the above-described problem. An objective of the present invention is to realize a medical material the surface of which is chemically modified with a biocompatible component, which does not causing the deterioration of the base material, and which exhibits stable biocompatibility for a long term.

[Means for Solving the Problems]

To achieve the above objective, according to the present invention, a surface of a medical material is coated with a diamond-like carbon film (DLC film), a biocompatible component is given to a surface of the coated DLC film, thereby imparting biocompatibility to the medical material.

Specifically, the first medical material of the present invention includes a biocompatible component chemically bonded to a surface of a diamond-like carbon film formed on a surface of a base material.

According to the first medical material, the biocompatible component is bonded to the surface of the DLC film formed on the surface of the base material. Therefore, excellent biocompatibility can be given to the surface of the DLC film. The biocompatible component is chemically bonded to the surface of the DLC film and does not readily separate from the surface of the DLC film. Since the DLC film is capable of a hard, dense coating over the surface of various base materials, the DLC film itself does not separate, so that deterioration of the base material itself can be suppressed. As a result, it is possible to realize a medical material which exhibits stable biocompatibility for a long term such that the biocompatible component does not separate.

An intermediate layer may be provided between the base material and the diamond-like carbon film to improve adhesion between the base material and the diamond-like carbon film. With such a structure, the surface of the base material can be more firmly coated with the DLC film. The intermediate layer is preferably an amorphous film containing silicon

and carbon as primary constituents.

In the medical material of the present invention, the base material is preferably a metal material, ceramic material, or macromolecular material, or a complex thereof.

In the first medical material, the biocompatible component of the present invention may be a polymer or oligomer introduced to the surface of the diamond-like carbon film by a graft polymerization. Also, the biocompatible component of the present invention may be bonded by a covalent bond on the surface of the diamond-like carbon film, or bonded by an ionic bond.

With such a structure, a medical material of which the biocompatible component is not separated from the DLC film can be surely obtained.

The biocompatible component preferably contains at least one functional group selected from a group consisting of an ethylene oxide group, a hydroxy group, a phosphate group, an amino group, an amido group, a phosphorylcholine group, a sulfone group, and a carboxyl group. With such functional groups contained, the biocompatibility can be surely given to the surface of the medical material.

Furthermore, the biocompatible component of the present invention may be a polymer formed by grafting vinylmonomers which contain fluorine to the surface of the diamond-like carbon film, or a molecule containing silicon.

The second medical material of the present invention includes a hydrophilic functional group introduced to a surface of a diamond-like carbon film formed on a surface of a base material. Even with such a structure, it is possible to achieve a medical material which exhibits stable biocompatibility for a long term.

A medical instrument according to the present invention uses the medical material of the present invention. With such a structure, it is possible to achieve a medical instrument which exhibits stable biocompatibility for a long term.

The medical instrument according to the present invention is preferably an instrument for medical implant, and may be a catheter, guide wire, stent, artificial cardiovalvular membrane, or artificial joint.

A method for fabrication the first medical material according to the present invention includes: a diamond-like carbon film formation step of forming a diamond-like carbon film on a surface of a base material; an activation step of generating on a surface of the diamond-like carbon film a reactive region which serves as a polymerization starting point; and a polymcrization step of polymerizing monomers using the polymerization starting point to graft the monomers to the surface of the diamond-like carbon film.

According to the method for fabrication the first medical material of the present invention, a reactive region is generated on the surface of the DLC film, and the monomers is polymerize with the reactive region as a polymerization starting point, thereby easily achieving a medical material exhibiting stable biocompatibility for a long term introduced on thc surface of the base material.

In the method for fabrication the first medical material, it is preferable that the method further includes, before the diamond-like carbon film formation step, an intermediate layer formation step of forming on the surface of thc base material an intermediate layer for improving adhesion between the base material and the diamond-like carbon film. With this configuration, the DLC film can be surely coated with the surface of the base material. Also, it is preferable that in the intermediate layer formation step, the intermediate layer is formed of an amorphous film containing silicon and carbon as primary constituents.

In the method for fabrication the first medical material, the polymerization starting point is preferably a free radical, and thc activation step is preferably a plasma irradiation step of irradiating the surface of the diamond-like carbon film with plasma. With this structure, the polymerization starting point is surely generated on the surface of the DLC film. Also, it

is preferably that the plasma irradiation step uses, as the plasma, argon, xenon, neon, helium, krypton, nitrogen, oxygen, ammonium, hydrogen, or water vapor.

A method for fabrication the second medical material according to the present invention includes: a diamond-like carbon film formation step of forming a diamond-like carbon film on a surface of a base material; a plasma irradiation step of irradiating a surface of the diamond-like carbon film with plasma to generate a reactive region on the surface of the diamond-like carbon film; and a surface treatment step of causing a reaction of the reactive region and a molecule containing oxygen to introduce a hydroxy group to the surface of the diamond-like carbon film. Even with such a structure, it is possible to realize a medical material which exhibits stable biocompatibility for a long term.

[Effects of the Invention]

According to the present invention, a biocompatible component is chemically bonded to a DLC film formed on a surface of a material for a medical material, and therefore, the biocompatible component does not separate from the medical material, and the material is prevented from being degraded. As such, a medical material which exhibits stable biocompatibility for a long term can be realized.

[Best Mode for Carrying Out the Invention]

From various aspects, the present inventors reviewed a medical material which can maintain biocompatibility for a long term without separating a biocompatible component bonded to a surface of a base material. As a result, they found that irradiating an inert DLC film, which has no reactivity in nature, with plasma, or the like, can activate the DLC film, so that monomers can be grafted to the surface of the DLC film by graft polymerization, or various functional groups can be introduced to the surface of the DLC film.

The present inventors also found that, for example, after the surface of a DLC film is formed on the surface of a base material, such as a metal, ceramic, resin, rubber, or the like, is

activated, a biocompatible component is chemically bonded to thc surface of the resultant DLC film by means of graft polymerization, covalent bond, ionic bond, or the like, a medical material which exhibits excellent biocompatibility for a long term can be realized wherein none of separation of the biocompatible component from the material surface and deterioration of the material occurs, and completed the present invention. Hereinafter, a structure of the present invention is describcd.

The base material used in the present invention is a base material of a medical material used for manufacturing a medical instrument which comes in contact with a living body or organic component, typically a catheter, guide wire, stent, artificial cardiovalvular membrane, and artificial joint, and is a metal material, a semiconductor material, such as silicon, or the like, a ceramic material, rubber, a polymeric material, such as a resin, or the like, or a complex thereof. The medical material includes materials used for medical instruments, such as wircs, tubes, plates, etc., one that obtained by processing any of thesc materials in the shape of a mcdical instrument, and one that is in the midst of the formation of the medical instrumcnt.

Although the type of the base material is not limited to anything particular, a metal, such as iron, nickel, chrome, copper, titanium, platinum, tungsten, tantalum, or thc like, can be used. Also, alloys of these metals, for example, stainless steel, such as SUS316L, or the like, a shape memory alloy, such as a Ti-Ni alloy, a Cu-Al-Mn alloy, or the like, other alloys, such as a Cu-Zn alloy, a Ni-Al alloy, a titanium alloy, a tantalum alloy, a platinum alloy, a tungsten alloy, or the like, can be used.

Alternatively, the base material may be an aluminum, silicon or zirconium oxide, silicon or zirconium nitride, ceramic or apatite, such as a carbide, or bioactive ceramic, such as bioglass, or the like. The base material may be a macromolecular resin, such as polymethyl methacrylate (PMMA), high density polyethylene, polyacetal, or the like, a

silicon polymer, such as polydimethylsiloxane, or the like, or a fluoric polymer, such as polytetrafluoroethylene, or the like.

The DLC film formed on the surface of the base material is a film formed of diamond-like carbon (which may contain a very small amount of any other component as an impurity). This film is very smooth and inert in nature. However, free radicals or ion species can be generated by irradiating the surface of the DLC film with plasma, or the like, and cleaving some of diamond (carbon to carbon) bonds on the surface. Accordingly, a biocompatible component can be grafted by graft polymerization to the surface of the DLC film, or various functional groups can be introduced to the surface of the DLC film by means of reactions with various substances after activation.

Although the surface of the base material has irregularities on the order of microscale or nanoscale, formation of a DLC film on the surface of the base material can achieve a smooth surface. With the smooth surface, it is possible to uniformly irradiate the surface of the base material with plasma, so that uniform graft polymerization can be performed over the surface of the base material. Since the DLC film is a very dense and hard film, a foreign component can be prevented from permeating the DLC film and deteriorating the base material.

In the present invention, the DLC film can be formed on the surface of the base material using a known method, such as sputtering, DC magnetron sputtering, RF magnetron sputtering, chemical vapor deposition (CVD), plasma CVD, plasma-based ion implantation, plasma-based ion implantation with superimposed RF and high-voltage pulses, ionic plating, arc ionic plating, ion beam deposition, laser ablation, or the like. The thickness of the DLC film is not limited to any particular thickness but is preferably in the range of 0.01 to 3 μm and, more preferably, in the range of 0.02 to 1 μm.

Although the DLC film can be directly formed on the surface of the base material, an

intermediate layer may be provided between the base material and the DLC film for more firmly adhering the base material and the DLC film. The material of the intermediate layer can be selected among various materials according to the type of the base material. Any known material, such as an amorphous film of silicon (Si) and carbon (C), an amorphous film of titanium (Ti) and carbon (C), an amorphous film of chromium (Cr) and carbon (C), or the like, can be used for the intermediate layer. The thickness of the intermediate layer is not limited to any particular thickness but is preferably in the range of 0.005 to 0.3 μm and, more preferably, in the range of 0.01 to 0.1 μm.

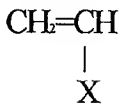
The intermediate layer can be formed using a known method. For example, sputtering, CVD, plasma CVD, flame spraying, ionic plating, arc ionic plating, or the like, may be used.

According to the present invention, the surface of a DLC film is activated by energy irradiation on the DLC film with plasma, light, or the like, whereby a radical, ion, or the like, which serves as a polymerization starting point, can be generated on the surface of the DLC film. In the case of plasma irradiation, a gas capable of disconnecting a carbon to carbon bond present on the surface of the DLC film, such as argon (Ar), neon (Ne), helium (He), krypton (Kr), xenon (Xe), nitrogen gas (N_2), oxygen gas (O_2), ammonium gas (NH_4), hydrogen gas (H_2), water vapor (H_2O), or the like, or a mixture gas thereof can be used as a plasma gas source. Alternatively, the surface of the DLC film can be activated by means of irradiation with ultraviolet light or ultraviolet ozone.

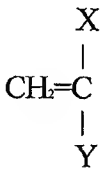
The activated surface of the DLC film has radicals, or the like, which serve as polymerization starting points. Therefore, various organic components can be grafted to the surface of the DLC film by graft-polymerizing various radical-polymerizable monomers on the activated surface of the DLC film. Therefore, an addition-polymerizable monomer, such as a vinylmonomer having the general formula of Formula 1, a vinylidene monomer having

the general formula of Formula 2, a vinylene monomer having the general formula of Formula 3, a cyclic vinylene monomer having the general formula of Formula 4, or the like, can be graft-polymerized at a polymerization starting point generated on the surface of the DLC film.

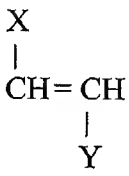
[Formula 1]



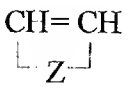
[Formula 2]



[Formula 3]



[Formula 4]



In the monomer structures of Formula 1 to Formula 3, substituents X and Y are ester or amido, typically -$COOR_1$, -$CONR_2$, or the like. Substituents X and Y in the same molecule may be identical or may be different. In the monomer structure of Formula 4, substituent Z is ester or amido which is a constituent of a cyclic structure and typically is -

CO-O-CO-, -CO-NR_3-CO-, or the like.

Especially in the case where the material is applied to medical uses, R_1 to R_3 are each has a structure containing a highly biocompatible constituent, for example, a functional group, such as an ethyleneoxide group, hydroxy group, amino group, phosphorylcholine group, phosphate group, sulfone group, nucleobase, or the like, a monosaccharide, or a polysaccharide. It is preferably a molecule which forms a hydrogel layer at the interface with water when graft-polymerized.

Other than hydrophilic monomers, it may be a monomer containing dimethylsiloxane, fluorine, or the like, which is unlikely to adsorb protein and exhibits high hydrophobicity and biocomparibility.

Specifically, a known polymerizable monomer from which a biocompatible polymer is obtained when graft polymerized, such as 2-methacryloyl-oxyethyl phosphorylcholine (MPC), 2-acryloyl-oxyethyl phosphorylcholine, 1-methyl-2-methacryloyl-amideethyl phosphorylcholine, 2-glucoxy-oxyethyl methacryl acid, sulfated 2-glucoxy-oxyethyl methacryl acid, p-N-vinylbenzyl-D-lactone amide, p-N-vinylbenzyl-D-propione amide, p-N-vinylbenzyl-D-malto-trione amide, o-methacryloyl-L-serine, o-methacryloyl-L-threonine, o-methacryloyl-L-tyrosine, o-methacryloyl-L-hydroxyproline, 2-methoxyethyl methacryl amide, 2-methoxyethyl acryl amide, 2-hydroxyethyl acryl acid, 2-hydroxyethyl methacrylic acid, N-2-hydroxypropyl methacryl amide, N-isopropyl acryl amide, N-vinylpyrrolidone, vinylphenol, N-2-hydroxy acryl amide, acryl amide derivative monomer, methacryl amide derivative monomer, phospholipid-like vinylmonomer, macromonomer of polyethylenoxyde, or the like, can be used.

For example, a hydrogel layer, which has the function of inhibiting recognition of a foreign substance by a living body similarly to the surface of a biomembrane, can be formed on the surface of a DLC film by introducing MPC to the surface of the DLC film by graft

polymerization. Since phospholipid present in blood is oriented/disposed on the basis of MPC grafted to the surface of the DLC film as a core, a function similar to that of the biomembrane can be given to the surface of the DLC film.

The above-listed monomers may be solely graft-polymerized or may be graft-polymerized in the form of a multidimensional copolymer. The graft polymerization may be performed at a single step or may be repeatedly performed in multi steps.

Although the optimum molecular weight of a polymer obtained by the graft polymerization depends on the use of the material, the type of a monomer to be grafted, etc., the component to be grafted to the surface is not limited to a macromolecule but may be an oligomer where the molecular weight of the polymer is 1000 or less. Especially when the material is applied to a medical use, the component may be one that the characteristics, such as the surface wettability of the material, etc., are changeable.

Since the polymerization starting points can be generated only on part of the surface of the DLC film subjected to energy irradiation, a polymer can be introduced by graft polymerization only at a desired position over the surface of the base material using an appropriate mask. Further, the density of the polymer on the surface of the base material can be freely adjusted.

Although the above-described example uses radical polymerization, the graft can be achieved with anion polymerization or cation polymerization instead of radical polymerization by generating cation species or anion species as polymerization starting points on the surface of the DLC film. These polymerization starting points can be generated by means of low-temperature plasma irradiation, ultraviolet or ultraviolet ozone irradiation, γ-ray, or the like.

The method for modifying with a functionality component the surface of the DLC film which serves as a coating over the surface of the base material is not limited to the graft

polymcrization of monomers. For example, the technique of grafting a molecular chain may be employed wherein, for example, a functional group, such as an amino group, a carboxyl group, or the like, is introduced to the surface of the DLC film, and the functional group introduced to the surface of the DLC film and a functional group of the molecular chain are brought into a reaction.

The surface of the DLC film is activated by, for example, a plasma treatment so that an active point, such as a radical, or the like, is generated, and then, the active point is brought into a reaction with water or oxygen, whereby a hydroxy group can readily be introduced to the surface of the DLC film.

The hydroxy group introduced to the surface of the DLC film can readily be converted into an amino group, a carboxyl group, an isocyanate group, or a vinyl group by means of a reaction with a functional alkoxy silane derivative, such as 3-aminopropyltrimethoxysilane, or the like, a functional carboxylic acid, such as 2-mercaptoacetic acid, or the like, a diisocyanate derivative, 2-mcthacryloyl-oxyethyl isocyanate, 2-acryloyl-oxyethyl isocyanate, N-methacryloyl-succinimide, or N-acryloyl-succinimide. A biocompatible component containing in the molecule a functional group which cause a reaction with the functional group introduced to the surface of the DLC film, for example, an amino group, a carboxyl group, an isocyanate group, or a trialkyloxysilane group such as trimethoxysilane, triethoxysilane, etc., can readily be covalent-bonded to the surface of the DLC film. Even when the biocompatible component does not include a functional group which causes a direct reaction with the functional group on the surface of the DLC film, a functional group can be covalent-bonded to the surface of the DLC film by using a bifunctional reagent.

In this case, a tissue-derived component having a functional group, such as peptide, protein, nucleobase, sugar chain, chitin, chitosan, or the like, or a biocompatible

macromolccular chain including a hydroxy group, a carboxyl group, or amino group introduced by chain transfer reaction at a terminal may bc brought into a coupling reaction with a functional group introduced to the surface of the DLC film in advance and fixed by covalent bond. The functionality component is not limited to a macromolecular chain but may be a low molecular component, such as an amino acid and a monosaccharide, and oligomers thereof. The reaction for converting the functional group is not limited to a single step reaction but may be a multi-step reaction. For example, the functional group may be converted in multi steps such that a hydroxy group is converted to an amino group and then to a vinyl group.

A biocompatible component may be introduced to the surface of the DLC film by forming an ionic bond between the surface of the DLC film and the biocompatible component using an ionic functional group present in the biocompatible component, such as a carboxyl group, amino group, phosphate group, or the like. In this case, the biocompatiblc component can readily be introduced to the surface of the DLC film even if it is an inorganic component, such as hydroxyapatitc, or the like.

Biocompatibility may be given to the DLC film itself by introducing a functional group to the surface of the DLC film to alter the surface of the DLC film into a hydrophilic surface instead of introducing another biocompatible component to the surface of the DLC film.

(Example)

Hereinafter, the present invention is described in more detail along with an example but is not limited to this example in any respect.

Coating of a DLC film over the base material is first described. In this example, an aluminum alloy (equivalent to JIS-8021 alloy) having a length of 50 mm, a width of 5 mm, and a thickness of 55 μm and polyethylene terephthalate (PET) were used for the base

material.

FIG. 1 is a schematic view of an ionic vapor deposition apparatus used in this example. The ionic vapor deposition apparatus is a commonly-employed ionic vapor deposition apparatus wherein benzene (C_6H_6) gas is introduced as a carbon source into a DC arc discharge plasma generator 2 provided inside a vacuum chamber to generate plasma, and the generated plasma is collided with a substrate 1 biased to a negative voltage, which is a subject of the coating, whereby the plasma is solidified over the substrate 1 to form a film.

The base material was set inside the chamber of the ionic vapor deposition apparatus shown in FIG. 1, and argon gas (Ar) at the pressure of 10^{-3} to 10^{-5} Torr was introduced into the chamber, and then, a bombardment cleaning was carried out for about 30 minutes wherein Ar ions were generated by electric discharge, and the generated Ar ions were collided with the surface of the base material.

Then, tetramethylsilane ($Si(CH_3)_4$) was introduced into the chamber to form, as an intermediate layer, an amorphous film having a thickness of 0.02 μm to 0.05 μm containing silicon (Si) and carbon (C) as primary constituents.

After the formation of the intermediate layer, C_6H_6 gas was introduced into the chamber, and the gas pressure was set to 10^{-3} Torr. Electric discharge was performed while C_6H_6 was continuously introduced at the rate of 30 ml/min to ionize C_6H_6. Then, ionic vapor deposition was performed for about 10 minutes to form a DLC film having a thickness of 0.1 μm over the surface of the base material.

The formation of the DLC film was carried out under the following conditions: Substrate Voltage 1.5 kV, Substrate Current 50 mA, Filament Voltage 14 V, Filament Current 30 A, Anode Voltage 50V, Anode Current 0.6 A, Reflector Voltage 50 V, Reflector Current 6 mA. The temperature of the substrate was about 160°C.

The intermediate layer was provided for improving the adherence between the base

material and the DLC film but may be omitted if sufficient adherence can be secured between the base material and the DLC film.

In this example, C_6H_6 gas was solely used as the carbon source, but mixture gas of C_6H_6 and fluorocarbon gas, such as CF_4, or the like, may be used for forming a DLC film containing fluorine over the surface of the base material.

The DLC film formed over the surface of the base material was irradiated with plasma to activate the surface, and then a functionality component was grafted to the surface of the DLC film. FIG. 2 is a schematic view of a plasma irradiation apparatus used in this example.

As shown in FIG. 2, the plasma irradiation apparatus is a commonly-employed plasma irradiation apparatus wherein a chamber 21 formed by a separable flask, to which a vacuum pump 22 is connected and with which gas replacement is possible, is provided with electrodes 23 and 24 at the barrel and bottom, respectively, and a high frequency wave is applied to the electrodes through a matching network from a high frequency source 26 to generate plasma inside the chamber 21.

Firstly, the base material 11 with the DLC film formed thereon was set inside the chamber 21 of the plasma irradiation apparatus, and Ar gas was introduced so that the inner pressure of the chamber 21 was 1.3 Pa. Then, a high frequency wave of 20 W was applied to the electrodes 23 and 24 using the high frequency source 26 (JRF-300 manufactured by JEOL Ltd.; Frequency 13.56 MHz) to generate plasma inside the chamber 21. The DLC film formed on the base material 11 was irradiated with the plasma for about 2 minutes to produce radicals on the surface of the DLC film.

After the plasma irradiation, the base material was exposed to air for about 1 minute and then inserted into a glass polymerization tube together with 10 ml of ethanol solution of hydrophilic 2-hydroxypropyl methacryl amide (HPMA) (concentration: 0.17 g/ml). The

cycle of freezing - deaeration - nitride replacement in liquid nitrogen was repeated several times to purge dissolved oxygen from the polymerization tube. Thereafter, the polymerization tube was sealed under a reduced pressure, and polymerization was carried out at 80°C for 24 hours, whereby HPMA was graft-polymerized over the surface of the DLC film to graft the polymer of HPMA.

After the polymerization, the base material was immersed into an abundant amount of ethanol and then washed with an abundant amount of phosphoric acid buffer solution (pH=7.4) before freeze drying. As a result, a graft base material with a grafted HPMA polymer was obtained. It should be noted that, after the plasma irradiation, the base material is not necessarily exposed to air.

We measured the composition of elements present at the surface of the obtained graft base material using X-ray photoelectron spectroscopy (XPS) and confirmed introduction of HPMA. The XPS measurement was carried out using a XPS/ESCA apparatus, Model 5600 CiMC, manufactured by Perkin Elmer, Inc., and the X-ray source was a monochromatized Alkα (1486.5 eV) at the power of 100 w (14 kV, 7 mA). In the measurement, a neutralizer was used as a neutralizing electron gun, and the depth of the measurement was 4 nm.

FIG. 3 shows the results of XPS measurement of the distribution of elements present at the surface of a DLC film formed on a base material of aluminum. FIG. 3(a) shows the result of a base material surface measurement before a HPMA polymer was grafted. FIG. 3(b) shows the result of a base material surface measurement after the HPMA polymer was grafted.

Referring to FIG. 3(b), as for the DLC film surface after the HPMA polymer graft, we found the 1s peak of nitrogen (N), which was not seen before the graft (FIG. 3(a)). The constitution ratio of carbon (C), oxygen (O), and nitrogen (N) obtained from the peak areas was C: 85.1%, O: 13.93%, N:0.89% before the graft, but C: 85.1%, O: 13.93%, N: 0.89%

after the graft. That is, nitrogen (N) and oxygen (O) were greatly increased with respect to carbon (C). This indicates that a HPMA polymer was grafted to the surface of the DLC film and, as a result, an amido group was introduced to the surface of the DLC film.

We also grafted a HPMA polymer to a DLC film formed on a base material of PET and carried out the above-described measurement on this sample. We also found the 1s peak of nitrogen after the HPMA polymer graft, which was not seen before the graft, and confirmed introduction of the HPMA polymer as in the case of the aluminum base material.

Then, the wettability of the surface of the obtained graft base material was measured using a contact angle measurement apparatus. The measurement of the contact angle was carried out using a goniometer-based contact angle measurement apparatus G-I manufactured by ERMA Inc.), wherein a water drop of 15 μl was placed on the surface of the medical material, and 50 seconds later, the left contact angle was measured, and 70 seconds later, the right contact angle was measured. The measurement value was the average of values at 10 measurement points.

In the case where a HPMA polymer was grafted to the surface of the DLC film formed on the aluminum base material, the contact angle of 67.8±3.5° before the graft of the HPMA polymer was decreased to 51.8±3.0° after the graft. This indicates that the HPMA polymer grafted to the surface of the DLC film changed the surface to be hydrophilic, thereby improving the biocompatibility of the graft base material.

In the case of the PET base material, the contact angle of 80.2±2.2° before the graft of the HPMA polymer was decreased to 52.1±2.5° after the graft. This indicates that the surface was changed to be hydrophilic as was in the case of the aluminum base material.

As described above, a polymer of HPMA is grafted to the surface of a DLC film formed on a medical material so that the surface of the DLC film becomes hydrophilic, whereby a hydrogel layer which inhibits foreign substance recognition by a living body is

formed on the surface of the DLC film. Therefore, the biocompatibility of the medical material is improved. Since the HPMA polymer is introduced to the surface of the DLC film by graft polymerization so as not to readily separate, stable biocompatibility can be maintained for a long term.

By using the procedure of this example, a hydrophilic hydroxy group can be introduced to the surface of a DLC film. A DLC film was treated with plasma according to the procedure of this example and subjected to an exposure treatment in air for 2 minutes. The resultant sample was subjected to the XPS measurement and contact angle measurement. In the XPS measurement, we saw a C1s peak based on C-O bonds near 287 eV, which was not seen in an untreated DLC film, and confirmed introduction of a hydroxy group. The contact angle of 79.2±3.0° before the plasma treatment was decreased to 69.8±3.2° after the plasma treatment, which means an improvement in the wettability of the surface of the DLC film. This indicates that exposure of the plasma-treated DLC film to air caused a reaction of radicals produced at the surface of the DLC film and oxygen in air, whereby a hydroxy group was introduced to the surface of the DLC film.

[Industrial Applicability]

According to a medical material, a medical instrument using thereof, and a method for fabricating the medical material, a biocompatible component is chemically bonded to a DLC film formed on a surface of a material for a medical material, and therefore, the biocompatible component does not separate from the medical material, and the material is prevented from being degraded. As such, a medical material which exhibits stable biocompatibility for a long term can be achieved. Therefore, the present invention is useful as a medical material that is in contact with a living body or organic component, and exhibiting excellent biocompatibility and a medical instrument using the medical material, and a method for fabricating the medical material.

[Bricf Description of the Drawing]

[Figure 1] FIG. 1 is a schematic view of an ionic vapor deposition apparatus according to an embodiment of the present invention.

[Figure 2] FIG. 2 is a schematic view of a plasma irradiation apparatus which is used for a medical material production method according to an embodiment of the present invention.

[Figure 3] FIG. 3(a) and FIG. 3(b) show results of XPS measurement of the surface of a DLC film formed on a base material of aluminum based on a medical material production method according to an embodiment of the present invention. FIG. 3(a) shows the measurement result obtained before HMPA graft. FIG. 3(b) shows the measurement result obtained after HMPA graft.

[Description of the Reference Numerals]

1	Substrate
2	Arc Discharge Plasma Generator
11	Base Material
21	Chamber
22	Vacuum Pump
23	Electrode
24	Electrode
25	High Frequency Power Supply
26	Matching Network

[Name of thc Document] Claims

[Claim 1] A medical material comprising a biocompatible component chemically bonded to a surface of a diamond-like carbon film formed on a surface of a base material.

[Claim 2] The medical material of claim 1, wherein an intermediate layer is provided between the base material and the diamond-like carbon film to improve adhesion between the base material and the diamond-like carbon film.

[Claim 3] The medical material of claim 2, wherein the intermediate layer is an amorphous film containing silicon and carbon as primary constituents.

[Claim 4] The medical material of any one of claims 1-3, wherein the base material is a metal material, ceramic material, or macromolecular material, or a complex thereof.

[Claim 5] The medical material of any one of claims 1-4, whcrein the biocompatible component is a polymer introduced by graft polymerization to the surface of the diamond-like carbon film.

[Claim 6] The medical material of any onc of claims 1-4, wherein the biocompatible component is an oligomer introduced by graft polymerization to the surface of the diamond-like carbon film.

[Claim 7] The medical material of any one of claims 1-4, wherein the biocompatible component is bonded by a covalent bond to the surface of the diamond-like carbon film.

[Claim 8] The medical material of any one of claims 1-4, wherein the biocompatible component is bonded by an ionic bond to the surface of the diamond-like carbon film.

[Claim 9] The medical material of any one of claims 1-8, wherein the biocompatible component contains at least one functional group selected from a group consisting of an ethylene oxide group, a hydroxy group, a phosphate group, an amino group, an amido group, a phosphorylcholine group, a sulfone group, and a carboxyl group.

[Claim 10] The medical material of claim 5 or 6, wherein the biocompatible component is a

polymer formed by grafting vinylmonomers which contain fluorine to the surface of the diamond-like carbon film.

[Claim 11] The medical material of claim 5 or 6, wherein the biocompatible component is a molecule containing silicon, the molecule being grafted to the surface of the diamond-like carbon film.

[Claim 12] A medical material, comprising a hydrophilic functional group introduced to a surface of a diamond-like carbon film formed on a surface of a base material.

[Claim 13] A medical instrument formed by using the medical material of any one of claims 1-12.

[Claim 14] The medical instrument of claim 13, wherein the medical instrument is a medical instrument which is to be embedded in a living body.

[Claim 15] The medical instrument of claim 14, wherein the medical instrument is a catheter, guide wire, stent, artificial cardiovalvular membrane, or artificial joint.

[Claim 16] A method for fabricating a medical material, the method comprising:

a diamond-like carbon film formation step of forming a diamond-like carbon film on a surface of a base material;

an activation step of generating on a surface of the diamond-like carbon film a reactive region which serves as a polymerization starting point; and

a polymerization step of polymerizing monomers using the polymerization starting point to graft the monomers to the surface of the diamond-like carbon film.

[Claim 17] The method of claim 16 further comprising, before the diamond-like carbon film formation step, an intermediate layer formation step of forming on the surface of the base material an intermediate layer for improving adhesion between the base material and the diamond-like carbon film.

[Claim 18] The method of claim 17 wherein, in the intermediate layer formation step, the

intermediate layer is formed of an amorphous film containing silicon and carbon as primary constituents.

[Claim 19] The method of any one of claims 16-18, wherein the activation step is the step of generating a free radical as the polymerization starting point.

[Claim 20] The method of any one of claims 16-18, wherein the activation step is a plasma irradiation step of irradiating the surface of the diamond-like carbon film with plasma.

[Claim 21] The method of claim 20, wherein the plasma irradiation step uses, as the plasma, argon, xenon, neon, helium, krypton, nitrogen, oxygen, ammonium, hydrogen, or water vapor.

[Claim 22] A method for fabricating a medical material, the method comprising:

a diamond-like carbon film formation step of forming a diamond-like carbon film on a surface of a base material;

a plasma irradiation step of irradiating a surface of the diamond-like carbon film with plasma to generate a reactive region on the surface of the diamond-like carbon film; and

a surface modification step of causing a reaction of the reactive region and a molecule containing oxygen to introduce a hydroxy group to the surface of the diamond-like carbon film.

[Name of the Document] Abstract

[Abstract]

[Object] The present invention can achieve a medical material which exhibits stable biocompatibility for a long term by introducing a biocompatible component to a DLC film formed on a surface of a base material.

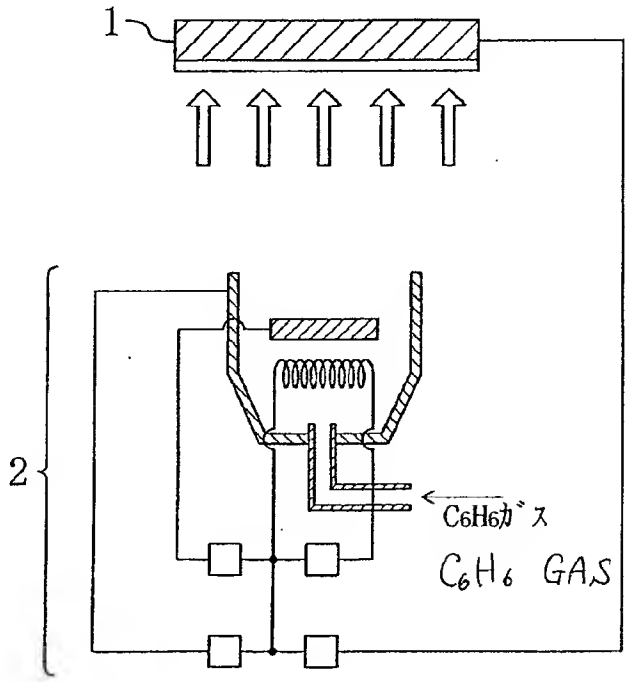
[Solution] A diamond-like carbon film (DLC film) is formed on a surface of a base material for a medical material. The surface of the resultant DLC film is treated with plasma, or the like, so as to be activated. Various monomers having biocompatibility, etc., are graft-polymerized to the activated surface of the DLC film, whereby a biocompatible component is bonded to the surface of the DLC film. Thus, it is possible to realize a medical material or a medical instrument which exhibits stable biocompatibility for a long term such that the biocompatible component does not separate from the surface of the base material.

[Selected Figure] None

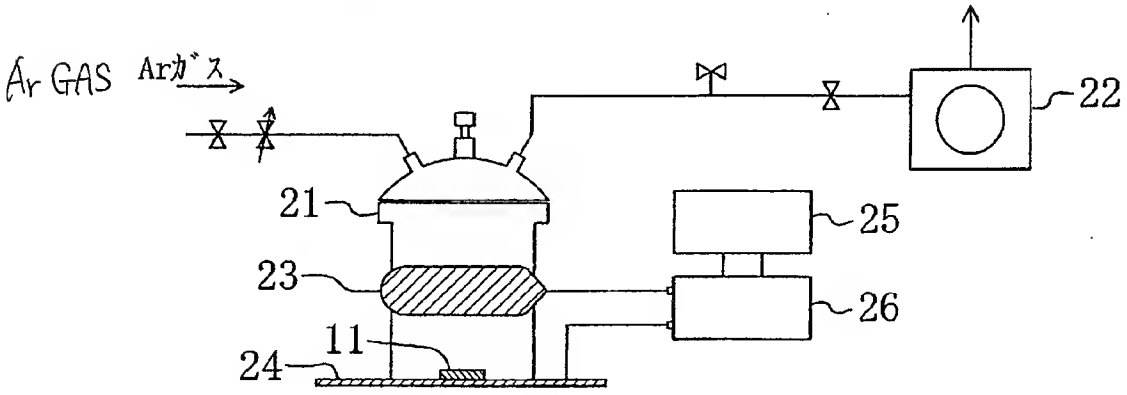
【書類名】図面 DRAWINGS

【図１】

FIGURE 1

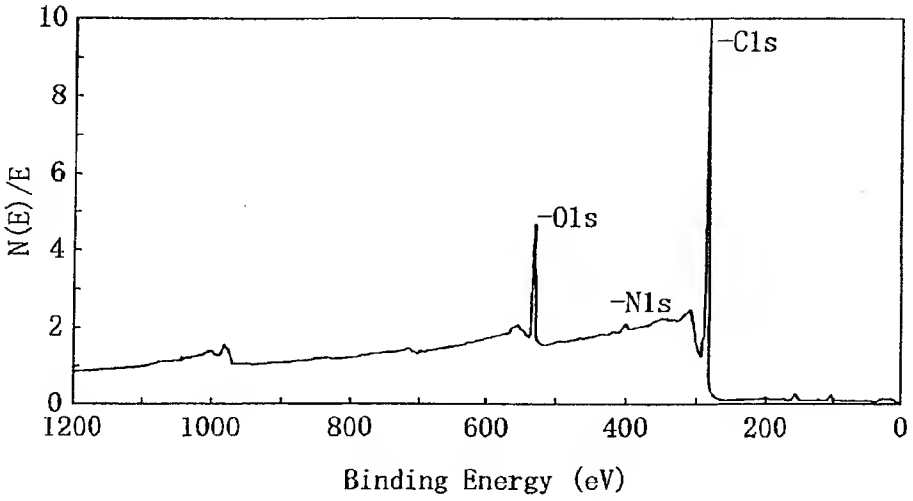


【図２】 FIGURE 2



【図3】 FIGURE 3

(a)



(b)